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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,363	08/14/2003	Jong-Wan Park	13100-02CIP	1639

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EXAMINER	
ROBERTS, LEZAH	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/642,363	PARK ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 21-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *A-E*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The office recognizes the provisional election of group I for the elected invention, and 2-hydroxymethyl-pyran-3,4,5-triol-6-yl for R_1 and hydrogen for R_2 and R_3 for the election of species, with traverse. The Applicant's arguments have been taken into consideration but are unpersuasive. Claims 7-20 will be examined on the merits. Claims 1-6 and 21-25 read on a nonelected species and invention and have been withdrawn from consideration.

Claims

Claim Rejections - 35 USC § 112 – Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of tumor growth with the mannose YC-1 derivative, does not reasonably provide enablement for inhibiting HIF-1a expression in tumor cells or tissues, inhibiting tumor growth, inhibiting HIF-1-regulated gene expression, inhibiting angiogenesis in tumor cells or

tissues, inhibiting tumor progression and metastasis treating a HIF-1- mediated disorder or condition by all polyol YC-1 derivatives claimed.

The claims have been analyzed by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention,
2) the breadth of the claims,
3) the relative skill of those in the art,
4) the state of the prior art,
5) the predictability of the art,
6) the amount of direction or guidance provided,
7) the presence or absence of working examples, and
8) the quantity of experimentation necessary.

The nature of the invention. The disclosed invention relates to inhibition of tumor growth, HIF-1a expression in tumor cells or tissues, HIF-1-regulated gene expression, angiogenesis in tumor cells or tissues, tumor progression and metastasis, and treating a HIF-1- mediated disorders or conditions related to several types of cancers by polyol YC-1 derivatives of Formula I.

The breadth of the claims. The claims are broad insofar as they read on inhibiting HIF-1 related functions related to various cancers with various polyol YC-1 derivatives.

The relative skill of those in the art. The relative skill of those in the art is high, generally that of a PHD or MD.

The state of the prior art. Prior art teaches the derivatives of a lead drug do not necessarily act with the same potency of the lead drug. Some derivatives have high efficacy and some have low to no efficacy at all towards the target function. Lee et al., J. of Med. Chem. 2001, teach the synthesis of several derivatives of YC-1 to test for antiplatelet activity. Out of all the derivatives synthesized and tested it was concluded only five of the indazole compounds showed promise as antiplatelet candidates out of about 31 compounds disclosed within the reference. Yeo et al., J. of the Natl. Can. Inst., discloses YC-1 as a potential anticancer drug targeting Hypoxia Inducible Factor I. Taking in consideration both of these references, just based on the knowledge that YC-1 targets HIF-I does not guarantee all its derivatives will act as adequate inhibitors. Testing one polyol with one test such as tumor growth does not provide substantial evidence that all the polyol derivatives will be effective in the above mentioned functions.

The predictability of the art. Based upon the prior art as discussed above, one cannot say if the all the derivatives of the instant claims will performed all the aforementioned functions if they are not screened. It cannot be predicted that all the polyol derivatives will be successful in performing the above mentioned functions.

The amount of direction or guidance provided. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the

invention as claimed. The specification does provide guidance for testing the YC-1 compound itself but does not provide adequate guidance for testing all the claimed polyol YC-1 derivatives claimed.

The presence or absence of working examples. The specification provides one working example in relation to the YC-1 polyols. It disclosed an experiment wherein an animal was injected with human hepatoma cells. The mannose polyol was administered to the animal and the effect on the tumor was observed. This was the only example relating to the polyol derivatives.

The quantity of experimentation necessary. Various experiments would need to be performed to give a good representation that the compounds claimed would indeed perform the above functions. This would involve screening each of the claimed compounds for all of the disclosed functions as well as for the different cancers mentioned.

2) Claims 7-20 are rejected under 35 U.S.C. 112 , first paragraph, because the specification, while being enabling for the inhibition of tumor growth with the mannose YC-1 derivative in hepatoma cells in a xenograft, does not reasonably provide enablement for inhibiting HIF-1a expression in tumor cells or tissues, inhibiting tumor growth, inhibiting HIF-1-regulated gene expression, inhibiting angiogenesis in tumor cells or tissues, inhibiting tumor progression and metastasis treating a HIF-1- mediated disorder or condition for all cancers by all polyol YC-1 derivatives claimed.

The claims have been analyzed by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention,
2) the breadth of the claims,
3) the relative skill of those in the art,
4) the state of the prior art,
5) the predictability of the art,
6) the amount of direction or guidance provided,
7) the presence or absence of working examples, and
8) the quantity of experimentation necessary.

The nature of the invention. The disclosed invention relates to inhibition of tumor growth, HIF-1a expression in tumor cells or tissues, HIF-1-regulated gene expression, angiogenesis in tumor cells or tissues, tumor progression and metastasis, and treating a HIF-1- mediated disorders or conditions related to several types of cancers by polyol YC-1 derivatives of Formula I.

The breadth of the claims. The claims are broad insofar as they read on inhibiting HIF-1 related functions related to various cancers with various polyol YC-1 derivatives.

The relative skill of those in the art. The relative skill of those in the art is high, generally that of a PHD or MD.

The state of the prior art. The prior art disclosed the trials of screening drug candidates for cancers and how there is no one drug that can broadly treat cancer. Further, both the treatment of cancer and or inhibition of angiogenesis in

a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting angiogenesis, as in claim 13-14 would be effective in a host in need thereof, such as a host suffering from cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from *in vitro* to *in vivo* protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1St column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

The predictability of the art. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

The amount direction or guidance provided. The specification discloses very little guidance in regards of using the claimed compounds in the HIF related functions. With regards to the prevention of metastasis, as related to claims 17

and 18, the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent metastasis. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art such as cancer therapy.

The amount of direction or guidance provided. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed. The specification does provide some guidance for testing the lead compound YC-1, but does not provide adequate guidance for testing all the claimed polyol YC-1 derivatives claimed with all the disclosed cancers.

The presence or absence of working examples. The specification provides one working example in relation to the YC-1 polyols. It disclosed an experiment wherein an animal is injected with human hepatoma cells. The mannose polyol was administered to the animal and the effects on the tumor were observed. This was the only example relating to the polyol derivatives. There were no experiments with other derivatives or with the mannose YC-derivative representing inhibiting HIF-1-related functions in cancers besides hepatoma. The above information disclosed in the prior art supports how critical it is to test each drug candidate to determine its activity against the different HIF-1 related functions.

The quantity of experimentation necessary. Various experiments would need to be performed in order to show the claimed compounds could inhibit all of the functions listed above. Experiments include testing the compounds in an animal model as well as testing in more evolved systems because the compounds may have different effects when used in an actual cancer patient and may not be as effective.

3) Claims 19-20 are rejected under 35 U.S.C. 112 , first paragraph, because the specification, while being enabling for treatment of hepatoma with the mannose YC-1 derivative, does not reasonably provide enablement for the treatment of all HIF-1-mediated disorder or conditions in a mammal with all polyol YC-1 derivatives.

The claims have been analyzed by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention,
2) the breadth of the claims,
3) the relative skill of those in the art,
4) the state of the prior art,
5) the predictability of the art,
6) the amount of direction or guidance provided,
7) the presence or absence of working examples, and
8) the quantity of experimentation necessary.

The nature of the invention. The disclosed invention relates to inhibition of tumor growth, HIF-1α expression in tumor cells or tissues, HIF-1-regulated gene expression, angiogenesis in tumor cells or tissues, tumor progression and metastasis, and treating a HIF-1- mediated disorders or conditions related to several types of cancers by polyol YC-1 derivatives of Formula I.

The breadth of the claims. The claims are broad insofar as they read on treating HIF-1-mediatited disorders and conditions with various polyol YC-1 derivatives.

The relative skill of those in the art. The relative skill of those in the art is high, generally that of a PHD or MD.

The state of the prior art. Just looking at a narrow scope of HIF-1-mediated disorders or conditions disclosed by the Applicant shows it is not certain whether a compound can treat these disorders without some form of screening and testing. The prior art disclosed the trials of screening drug candidates for cancers and how there is no one drug that can broadly treat cancer. Further, both the treatment of cancer and or inhibition of angiogenesis in a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting angiogenesis, as in claim 13-14 would be effective in a host in need thereof- such as a host suffering from cancer. Further, treatment of cancer in

general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1St column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

The predictability of the art. Based upon the above findings, it would not be predictable that the method would function as contemplated. One could not undoubtedly say if all the derivatives of the instant claims can be used to treat all HIF-mediated disorders or conditions if they are not screened or tested in a human subject.

The amount of direction or guidance provided. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would require undue experimentation by one of skill in the art to practice the invention as claimed. The specification does provide some guidance for testing the lead compound YC-1, but does not provide adequate guidance for testing all the claimed polyol YC-1 derivatives claimed.

The presence or absence of working examples. The specification provides one working example in relation to the YC-1 polyols. It disclosed an experiment wherein an animal was injected with human hepatoma cells. The mannose polyol

was administered to the animal and the effects on the tumor were observed. This was the only example relating to the polyol derivatives. There were no experiments with other derivatives or with the mannose YC-derivative representing inhibition of the above functions in different types of cancers. The above information disclosed in the prior art supports how critical it is to test each drug candidate to determine its ability to treat all HIF-1-mediated disorders or conditions.

The quantity of experimentation necessary. Various experiments would need to be performed to in order to show the claimed compounds could treat the various HIF-mediated disorders. Experiments include testing the compounds in an animal model as well as testing in more evolved systems because the compounds may have different effects when used in an actual cancer patient and may not be as effective.

Claim Rejections - 35 USC § 112 - Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. The claim uses the term "HIF-mediated" yet it does not specifically point out if the disorder is mediated positively or negatively. Interpreting the claims as is suggest the compound can

affect the disorder both positive and negatively, which is highly unlikely. The claim does not define the metes and bound to which the invention applies.

Claims 7-20 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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